REMARKS

Claims 1, 3, 4, 6-13, 17, 19, 20, and 22-25 are pending in the application. Claims 2, 5, 14-16, 18, 21, and 26-37 have been cancelled without prejudice, and claims 1, 3, 4, 11-13, 17, 19, 20, and 23-25 have been amended. Support for the amendments can be found in original claims 2 and 18 and in the specification at, e.g., page 3, lines 3-5; page 4, lines 16-18; page 15, lines 12-16; page 19, line 7, to page 20, line 8; and page 26, line 21, to page 27, line 12. These amendments add no new matter.

Title

On page 2 of the Office Action, the Examiner asserted that the title of the application is not descriptive and requested that applicants provide a new title that is indicative of the invention to which the claims are directed. The title of the application has been amended to the following: "Methods of Modulating T Cell or Natural Killer Cell Activity with Anti-P-Selectin Glycoprotein Ligand 1 Antibodies."

Amendments to the Specification

On page 2 of the Office Action, the Examiner requested correction of the spelling of the mouse species "BALB/c." This correction has been made throughout the specification. Applicants have not identified any other errors in the specification.

35 U.S.C. §112, First Paragraph (Written Description)

On pages 3-5 of the Office Acton, the Examiner rejected claims 1, 4-6, 10-15, 17, and 20-26 as allegedly containing subject mater that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention. According to the Examiner,

> [t]here is insufficient written description encompassing "a compound that binds to PSGL-1" and an agent that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of T cell" because the relevant identifying characteristics such as structure of other physical and/or

> chemical characteristics of both the "compound that binds to PSGL-1" and the "agent that binds to the monoclonal antibody", are not set forth in the specification as filed, commensurate in scope with the claimed invention. (emphasis in original)

Claims 5, 14, 15, 21, and 26 have been cancelled without prejudice, thereby rendering their rejection moot.

As amended, independent claims 1 and 17 recite "an antibody or antigen-binding fragment thereof that specifically binds to PSGL-1" (the term "compound" has been removed from the claims). The amendments to claims 1 and 17 incorporate the limitations of cancelled dependent claims 2 and 18, which were not rejected under this heading. It is applicants' understanding that these amendments overcome the rejection of independent claims 1 and 17 and dependent claims 6, 10-13, and 22-25.

As amended, dependent claims 4 and 20 recite an "antibody" that binds to an anti-PSGL-1 monoclonal antibody and induces cross-linking of a plurality of PSGL-1 antigens on the surface of a T cell or NK (the term "agent" has been removed from these claims). PSGL-1 cross-linking antibodies are described in the specification at, e.g., page 19, line 7, to page 20, line 8 (anti-hamster cross-linker antibody) and page 26, line 21, to page 27, line 12 (anti-mouse cross-linker antibody). The specification's description of exemplary anti-PSGL-1 cross-linking antibodies permits the person of ordinary skill in the art to conclude that the inventors invented the subject matter that is claimed and had possession of the claimed invention at the time the application was filed. Accordingly, applicants respectfully request that the Examiner withdraw the rejection.

35 U.S.C. §112, First Paragraph (Enablement)

On pages 5-8 of the Office Action, the Examiner rejected claims 1, 4-6, 10-15, 17, and 20-26 as allegedly not enabled. According to the Examiner,

> the specification, while being enabling for "anti-PSGL-1 antibodies" and anti-hamster Ig", does not reasonably provide enablement for any "compound that binds to PSGL-1" and any "agent that binds to the monoclonal antibody and

> induces the cross-linking of a plurality of PSGL-1 antigens on the surface of T cell" (emphasis in original)

Claims 5, 14, 15, 21, and 26 have been cancelled without prejudice, thereby rendering their rejection moot.

As detailed above, independent claims 1 and 17 have been amended to incorporate the limitations of cancelled dependent claims 2 and 18 (which were not rejected under this heading) and recite "an antibody or antigen-binding fragment thereof that specifically binds to PSGL-1." It is applicants' understanding that these amendments overcome the rejection of independent claims 1 and 17 and dependent claims 6, 10-13, and 22-25.

Also as detailed above, dependent claims 4 and 20 have been amended to recite an "antibody" that binds to an anti-PSGL-1 monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of a T cell or NK cell (the term "agent" has been removed from the claims). Cross-linking antibodies (such as the exemplary cross-linker antibodies described in the specification at page 19, line 7, to page 20, line 8 and page 26, line 21, to page 27, line 12) were well known to the person of ordinary skill in the art and in common usage at the time of filing of the present application. Accordingly, the skilled artisan would have been able to practice the claimed methods without undue experimentation and with a reasonable expectation of success. In view of these amendments, applicants respectfully request that the Examiner withdraw the rejection.

On pages 8-11 of the Office Action, the Examiner rejected claims 1-6 and 10-26 as allegedly not enabled. According to the Examiner,

> the specification, while being enabling for methods of reducing T cell mediated immune responses in an individual (including method of treating diabetes as the elected invention) and methods of inducing death of a T cell or a NK cell with anti-PSGL-1 antibodies in vivo (the elected invention), does not reasonably provide enablement for methods of "preventing diabetes" nor "methods of preventing or reducing T cell mediated immune responses in an individual (i.e., in vivo, clinically) with "agent that binds to the monoclonal antibody and induces the cross-linking of plurality of PSGL-1 antigens on the surface of T cell",

including the use of the exemplified "anti-hamster Ig." (emphasis in original)

Claims 2, 5, 14-16, 18, 21, and 26 have been cancelled without prejudice, thereby rendering their rejection moot.

As amended, independent claims 1 and 17 are directed to methods of using "an antibody or antigen binding fragment thereof that specifically binds to PSGL-1" to reduce a T cell mediated response in an individual (claim 1) or induce the death of a T cell or NK cell (claim 17). In view of the Examiner's statement in the passage reproduced above regarding enabled subject matter, it is applicants' understanding that these amendments overcome the rejections of independent claims 1 and 17 and dependent claims 3, 6, 10-13, 19, and 22-25.

In addressing enablement for the subject matter of dependent claims 4 and 20, the Examiner stated that

> [t]he specification does not adequately teach how to effectively treat any T cell mediated immune response in an individual, including the elected autoimmune diseases and diabetes or reach any therapeutic endpoint in humans by administering "anti-PSGL-1 antibody" and an "agent that binds to the monoclonal antibody and induces the cross-linking of plurality of PSGL-1 antigens on the surface of T cell", including the use of the exemplified "anti-hamster Ig" that results in a signal transduction pathway that results in the death of a T cell.
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> Further, it is noted that Examples 6-8 on pages 22-25 of the instant specification which rely upon the administration of anti-PSGL-1 antibodies do not rely on the administration of an "agent that binds to the monoclonal antibody and induces the cross-linking of plurality of PSGL-1 antigens on the surface of T cell.
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> For example, the anti-hamster Ig cross-linking agent exemplified in the specification as filed was only employed under defined in vitro conditions and not under in vivo conditions. A sufficient amount of anti-hamster Ig would not have been expected to reach and cross-link anti-PSGL-1 antibody resulting in the death of T cells and NK cells encompassed by the claims and intended by the specification.

> For example, anti-PSGL-1 antibodies would have been expected to bind a number of cells types and not just anti-PSGL-1 antibodies that bind PSGL-1 expressed on T cells. The administration of "anti-hamster Ig" would likely have resulted in eliciting neutralizing antibodies in the individual under treatment. It would have been unpredictable at the time the invention was made that an "agent, including as anti-hamster Ig", would have reached the targeted T cell populations in sufficient quantity and quality to cross-link anti-PSGL antibodies on said T cells and, in turn, result in T cell death. Applicant has not provided sufficient working examples to support this assertion and disclosure. As indicated, the instant Examples do not rely upon the claimed methods which rely upon a secondary agent. (emphasis in original)

As noted above, it is applicants' understanding that the amendments to independent claims 1 and 17 overcome the enablement rejections for these claims.

The skilled artisan would have had no reason to expect that the effectiveness of the methods of independent claims 1 and 17 would have been negated by, in addition to the steps recited in those claims, also administering to the individual a cross-linking antibody (claim 4) or contacting the monoclonal antibody with a cross-linking antibody (claim 20).

The specification contains working examples demonstrating the effectiveness of administration of an agonist anti-PSGL-1 antibody in depleting T cells in an animal (Example 6), reducing transplant rejection in an animal (Example 8), and delaying the onset of experimental autoimmune diabetes in an animal (Example 11). In addition, the specification demonstrates that T cells can be depleted *in vitro* by contacting T cells with an agonist anti-PSGL-1 antibody and a cross-linker antibody, thereby inducing apoptosis in the T cells (Examples 3 and 10).

Without being bound to any theory, applicants believe that the T cell depletion that occurs *in vivo* following administration to an individual of an agonist anti-PSGL-1 antibody results, at least in part, from cross-linking of the administered antibody by endogenous components of the individual's immune system, such as Fc receptor bearing cells (which bind to and cross-link administered antibodies that have bound to the surface of cells). The addition of a cross-linker antibody in applicants' *in vitro* experiments is believed to serve the same cross-linking function as Fc receptor bearing cells *in vivo*. The use of cross-linking antibodies *in vitro* is a standard technique for approximating cross-linking that occurs naturally *in vivo*.

In view of the foregoing, the skilled artisan would have expected the addition of a cross-linker antibody to an individual to merely supplement the cross-linking that occurs naturally via the individual's endogenous Fc receptor bearing cells. Accordingly, the person of ordinary skill in the art, at the time the present application was filed, would have been able to carry out the method of dependent claims 4 and 20 without undue experimentation and with a reasonable expectation of success. Applicants request that the Examiner withdraw the rejection.

Claim Objections

On page 11 of the Office Action, the Examiner objected to claims 11, 12, 15, 16, 23, and 24 as allegedly reciting improper designations for CD3, CD4, and CD8. Claim 15 has been cancelled without prejudice, thereby rendering its objection moot. Claims 11, 12, 16, 23, and 24 have been amended to recite the superscript designations requested by the Examiner.

35 U.S.C. §112, Second Paragraph (Indefiniteness)

On page 11 of the Office Action, the Examiner rejected claims 13, 14, 25, and 26 as allegedly indefinite. According to the Examiner, the claims

> do not set forth clearly the method steps to carry out "the claimed methods of "detecting the number of T cells in a first biological sample", "detecting a biological activity of T cells in a first biological sample" and "assessing viability". The claims are incomplete as they omit essential steps and endpoints to carry out the claimed methods of detection.

Claims 14 and 26 have been cancelled without prejudice, thereby rendering their rejection moot.

Applicants traverse the rejection of claims 13 and 25.

Claim 13 recites two steps: (1) detecting the number of T cells in a first biological sample taken from the individual before the administration of the composition; and (2) comparing the number of T cells detected in the first biological sample with the number of T cells in a second biological sample taken from the individual after the administration of the composition. The skilled artisan at the time the present application was filed would have readily understood that

the "detecting" step of claim 13, to which the Examiner raised the rejection, can be performed by standard routine cell counting techniques (e.g., by determining the number of cells in a blood sample that exhibit a T cell surface marker such as CD3). The metes and bounds of this claim are clear and the claim omits no essential steps.

Claim 25 requires a step of assessing the viability of a T cell or NK cell after contacting the cell with the antibody or antigen-binding fragment thereof. This step allows for confirmation that the antibody or antigen-binding fragment thereof has resulted in the death of the T cell or NK cell. Means of assessing the viability of cells (e.g., 7-AAD viability staining, as disclosed in the specification at page 19, lines 13-21) are well known to those of skill in the art. The metes and bounds of this claim are clear and the claim does not omit any essential steps.

35 U.S.C. §102(b) (Anticipation)

On pages 12-13 of the Office Action, the Examiner rejected claims 1-3, 6, 10-12, 15-19, and 22-24 as allegedly anticipated by Larsen et al., U.S. Patent No. 5,840,679 ("Larsen"). According to the Examiner,

> Larsen et al. teaches methods of treating conditions characterized by P-selectin mediated intercellular adhesion, including inflammatory conditions, autoimmune conditions such as diabetes (see columns 15-16, overlapping paragraph) with neutralizing anti-PSGL-1 antibodies, including monoclonal antibodies (e.g. see column 18, paragraphs 2-4).
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> Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations, including the targeted cell populations and the mechanism of action, would be inherent properties of the referenced methods to treat a number of conditions and diseases with anti-PSGL-1 antibodies, which block the P-selectin ligand adherence function, abolish or markedly reduce inflammation (e.g. see columns 18-19, overlapping paragraph). Here, too, it is noted that target cells targeted by anti-PSGL-1 antibody may be eliminated by ADCC (see column 19, lines 5-13).
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> Also, the Courts have held that there is no requirement that those of ordinary skill in the art know of the inherent property. See MPEP 2131.01(d) and MPEP §2112 – §2113 for case law on inherency.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. (emphasis added)

Claims 2, 15, and 18 have been cancelled without prejudice, thereby rendering their rejection moot.

Applicants respectfully traverse the rejection of the remaining claims in view of the claim amendments and the following comments.

The currently claimed invention is based, at least in part, on applicants' discovery that certain antibodies directed against the T cell surface molecule PSGL-1 can induce T cells to undergo apoptosis and effect T cell depletion in an individual. T cell depletion can be particularly useful for the treatment of conditions associated with an excessive or unwanted T cell-mediated immune response or excessive or unwanted T cell proliferation. Examples of such conditions include autoimmune diseases, transplant rejection, allergic diseases, and T cell-derived cancers.

The independent claims are directed to methods of reducing a T cell-mediated immune response in an individual (claim 1) and inducing the death of a T cell or NK cell (claim 17). Each of the claimed methods recites a step requiring the use of an antibody that binds to PSGL-1 on the surface of a T cell or NK cell, wherein the binding of the antibody to PSGL-1 on the surface of the cell induces a signal transduction pathway that results in the death of the T cell or NK cell.

As noted in the passage reproduced above from the Office Action, Larsen discloses methods of using a neutralizing anti-PSGL-1 antibody to treat certain conditions. According to Larsen, the neutralizing antibody used therein blocks "the selectin mediated intercellular adherence function of the P-selectin ligand protein" (Larsen at column 18, lines 57-65). The neutralizing effect of Larsen's antibodies abolishes or reduces the adherence of leukocytes to sites of inappropriate inflammation (Larsen at column 18, line 65, to column 19, line 1).

The antibody of the claimed methods binds to PSGL-1 on the surface of a T cell or NK cell and induces a signal transduction pathway that results in the death of the cell (i.e., it is an

agonist antibody). By contrast, the anti-PSGL-1 antibody of Larsen is an antagonist antibody (it neutralizes the biological function of PSGL-1 by inhibiting binding of the receptor to P-Selectin). Larsen nowhere describes the use of an anti-PSGL-1 agonist antibody.

The Examiner asserted that the properties of the antibody recited in the claims are inherent in the antibody of Larsen. To rely on inherency, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." (MPEP § 2112, citing Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)) (emphasis in original). "Inherency, however, may not be established by probabilities or possibilities." (MPEP § 2112, citing In re Robertson, 169 F.3d 743, 745 (Fed. Cir. 1999)). "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." (MPEP § 2112, citing In re Rijckaert, 9 F.3d 1531, 1534 (Fed. Cir. 1993)) (emphasis in original).

The mechanism of action of the antibody recited in the claims is not one that is necessarily present in the antibody described by Larsen. Larsen's neutralizing anti-PSGL-1 antibody down regulates an immune response by neutralizing the binding of P-Selectin to PSGL-1. There is nothing to suggest that Larsen's antagonist antibody also acts by the distinct agonist mechanism of action recited in the claims. Applicants have discovered that particular anti-PSGL-1 antibodies can be made that induce apoptosis of PSGL-1 expressing cells. Not all anti-PSGL-1 antibodies possess this agonist function. Accordingly, there is no basis in fact or technical reasoning to reasonably conclude that the antibody of Larsen necessarily possesses the property of the antibody recited in the claimed methods.

For the foregoing reasons, Larsen does not anticipate the methods of claims 1 and 17. Applicants request that the Examiner withdraw the rejections of independent claims 1 and 17 and the claims that depend therefrom be withdrawn.

35 U.S.C. §103(a) (Obviousness)

On pages 13-16 of the Office Action, the Examiner rejected claims 1-3, 6, 10-19, and 22-26 as allegedly unpatentable over Larsen in view of Trembleau (1999) J. Immunol. 163:2960-68 ("Trembleau"), Yago et al. (1998) J. Immunol. 161:1140-45 ("Yago"), Hirata et al. (2000) J. Exp. Med. 192:1669-75 ("Hirata"), and Cobbold et al., U.S. Patent No. 6,056,956 ("Cobbold"). According to the Examiner,

> the prior art clearly provides for the administration of anti-PSGL-1 antibody to inhibit adhesion via PSGL-1/P-selectin interactions, inflammation and autoimmunity, including diabetes (elected species). While the prior art does not explicitly teach the induction of T cell or NK cell death, the prior art clearly provides for the same or nearly the same endpoints by administering the same antagonists to the same patient populations encompassed by the claimed methods. Again, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure
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> Given the teachings of the prior art that PSGL-1 was expressed on T cells, including T cells involved in inflammation and autoimmunity such as diabetes, as taught by Trembleau et al. and Hirata et al. in conjunction with the teachings of treating inflammation with anti-PSGL-1 antibodies as taught by Larsen et al., the ordinary artisan would have been motivated to monitor the presence and function of T cells as a result of anti-PSGL-1 treatment. Hirata et al. and Cobbold et al. both teach monitoring T cell numbers and function in response to the administration of antagonistic antibodies in vivo, including the administration of anti-PSGL-1. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to detect the number, viability and biological activity of T cells prior to and after the administration of antagonistic anti-PSGL-1 antibody in inflammatory or autoimmune conditions such as diabetes to monitor to efficacy of antibody treatment, including measuring the control values prior to treatment. (emphasis added)

Claims 2, 14-16, 18, and 26 have been cancelled without prejudice, thereby rendering their rejection moot.

Applicants respectfully traverse the rejection of the remaining claims in view of the claim amendments and the following comments.

As detailed above in response to the 35 U.S.C. § 102(b) rejection, Larsen does not describe the use of an anti-PSGL-1 agonist antibody to reduce an immune response or to induce the death of a T cell or NK cell. Instead, the disclosure of Larsen is limited to methods that use a PSGL-1 antagonist antibody. Furthermore, the agonist function of the antibody recited in the claims is a feature that is not necessarily present in an antagonist anti-PSGL-1 antibody (i.e., not all anti-PSGL-1 antibodies can induce apoptosis of T cells).

A person of ordinary skill in the art at the time the present application was filed would have had no reason to modify the methods of Larsen to use a PSGL-1 agonist antibody in place of the PSGL-1 antagonist antibody described therein. Larsen teaches neutralizing PSGL-1 activity as a means to treat disease. Larsen gives no hint that inducing a signal transduction pathway via PSGL-1 can reduce an immune response in an individual or induce the death of a T cell or NK cell.

Trembleau, Yago, Hirata, and Cobbold do not add what is lacking in Larsen. In particular, none of these references suggests that an antibody that binds to PSGL-1 and induces a signal transduction pathway can be used to reduce an immune response or induce the death of a T cell or NK cell. As noted by the Examiner above, the cited references at best suggest antagonizing PSGL-1 function as a means to regulate an immune response. None of the references suggests the use of an agonist anti-PSGL-1 antibody, as is required by the claimed methods.

For the foregoing reasons, the cited references do not render obvious independent claims 1 or 17 or the claims that depend therefrom. Applicants request that the Examiner withdraw the rejection.

CONCLUSIONS

Applicants submit that all grounds for rejection have been overcome, and that all claims are in condition for allowance, which action is requested.

Please apply any charges or credits to deposit account 06-1050, referencing Attorney Docket No. 13062-003001.

Respectfully submitted,

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